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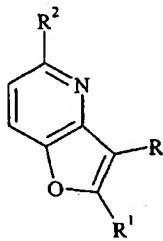
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(54) Title: 5-HT_{1F} AGONISTS



(I)

(57) Abstract

The present invention relates to a compound of formula (I) or a pharmaceutical acid addition salt thereof; which are useful for activating 5-HT_{1F} receptors and inhibiting neuronal protein extravasation in a mammal.

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5-HT_{1F} AGONISTS

Theories regarding the pathophysiology of migraine have been dominated since 1938 by the work of Graham and Wolff.

5 *Arch. Neurol. Psychiatry*, 39:737-63, 1938. They proposed that the cause of migraine headache was vasodilatation of extracranial vessels. This view was supported by knowledge that ergot alkaloids and sumatriptan, a hydrophilic 5-HT₁ agonist which does not cross the blood-brain barrier,

10 contract cephalic vascular smooth muscle and are effective in the treatment of migraine. Humphrey, et al., *Ann. NY Acad. Sci.*, 600:587-600, 1990. Recent work by Moskowitz has shown, however, that the occurrence of migraine headaches is independent of changes in vessel diameter. *Cephalgia*,

15 12:5-7, 1992.

Moskowitz has proposed that currently unknown triggers for pain stimulate trigeminal ganglia which innervate vasculature within the cephalic tissue, giving rise to release of vasoactive neuropeptides from axons on the

20 vasculature. These released neuropeptides then activate a series of events, a consequence of which is pain. This neurogenic inflammation is blocked by sumatriptan and ergot alkaloids by mechanisms involving 5-HT receptors, believed to be closely related to the 5-HT_{1D} subtype, located on the

25 trigeminovascular fibers. *Neurology*, 43(suppl. 3):S16-S20 1993.

Serotonin (5-HT) exhibits diverse physiological activity mediated by at least seven receptor classes, the most heterogeneous of which appears to be 5-HT₁. A human

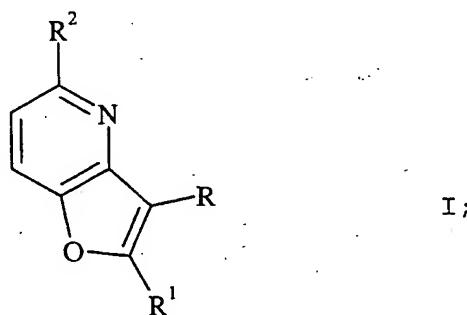
30 gene which expresses one of these 5-HT₁ receptor subtypes, named 5-HT_{1F}, was isolated by Kao and coworkers. *Proc. Natl. Acad. Sci. USA*, 90:408-412, 1993. This 5-HT_{1F} receptor exhibits a pharmacological profile distinct from any serotonergic receptor yet described. The high affinity

of sumatriptan at this subtype, $K_i=23$ nM, suggests a role of the 5-HT_{1F} receptor in migraine.

This invention relates to novel 5-HT_{1F} agonists which inhibit peptide extravasation due to stimulation of the 5 trigeminal ganglia, and are therefore useful for the treatment of migraine and associated disorders.

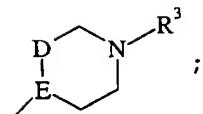
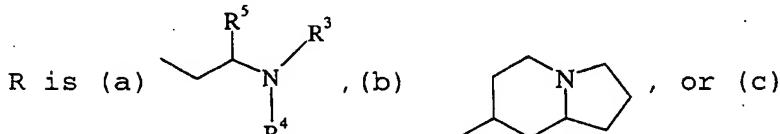
The present invention relates to a compound of formula I:

10



15

and pharmaceutical acid addition salts thereof, where;



E-D is C=CH or CH-CH₂;

R¹ is hydrogen or C₁-C₄ alkyl;

R² is hydrogen, halo, hydroxy, -NR³R⁴, -SR³, -C(O)R³,
20 -C(O)NR³R⁴, -NR³SO₂R⁵, -NHC(Q)NR³R⁴, -NHC(O)OR³, or
-NR³C(O)R⁵;

R³, R⁴, and R⁵ are independently hydrogen, C₁-C₄ alkyl,
C₂-C₆ alkenyl, C₂-C₆ alkynyl, or -(CH₂)_naryl; or R³ and R⁴

combine, together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, piperazine, 4-substituted piperazine, morpholine, or thiomorpholine ring:

n is 0, 1, 2, 3, 4, 5, or 6; and
5 Q is O or S.

This invention also relates to a pharmaceutical formulation comprising a compound of formula I, or a pharmaceutical acid addition salt thereof, and a 10 pharmaceutical carrier, diluent, or excipient.

In addition, the present invention relates to a method for activating 5-HT_{1F} receptors in mammals comprising administering to a mammal in need of such activation an effective amount of a compound of formula I, or a 15 pharmaceutical acid addition salt thereof.

Moreover, the current invention relates to a method for inhibiting neuronal protein extravasation comprising administering to a mammal in need of such inhibition an effective amount of a compound of formula I, or a 20 pharmaceutical acid addition salt thereof.

One embodiment of this invention is a method for increasing activation of the 5-HT_{1F} receptor for treating a variety of disorders which have been linked to decreased neurotransmission of serotonin in mammals. Included among 25 these disorders are depression, migraine pain, bulimia, premenstrual syndrome or late luteal phase syndrome, alcoholism, tobacco abuse, panic disorder, anxiety, general pain, post-traumatic syndrome, memory loss, dementia of aging, social phobia, attention deficit hyperactivity 30 disorder, disruptive behavior disorders, impulse control disorders, borderline personality disorder, obsessive compulsive disorder, chronic fatigue syndrome, premature ejaculation, erectile difficulty, anorexia nervosa, disorders of sleep, autism, mutism, trichotillomania,

trigeminal neuralgia, dental pain or temperomandibular joint dysfunction pain. The compounds of this invention are also useful as a prophylactic treatment for migraine. Any of these methods employ a compound of formula I.

5 The use of a compound of formula I for the activation of the 5-HT_{1F} receptor, for the inhibition of peptide extravasation in general or due to stimulation of the trigeminal ganglia specifically, and for the treatment of any of the disorders described above, are all embodiments of
10 the present invention.

The general chemical terms used throughout have their usual meanings. For example, the term "C₁-C₄ alkyl" refers to methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl and cyclobutyl. The term
15 "C₁-C₆ alkyl" includes those groups listed for C₁-C₄ alkyl and also refers to saturated, straight, branched, or cyclic hydrocarbon chains of 5 to 6 carbon atoms. Such groups include, but are not limited to, pentyl, pent-2-yl,
pent-3-yl, neopentyl, hexyl, and the like. The term "C₃-C₈
20 cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

The term "C₂-C₆ alkenyl" refers to mono-unsaturated straight or branched hydrocarbon chains containing from 2 to 6 carbon atoms and includes, but is not limited to, vinyl,
25 allyl, 1-buten-4-yl, 2-buten-4-yl, 1-penten-5-yl,
2-penten-5-yl, 3-penten-5-yl, 1-hexen-6-yl, 2-hexen-6-yl,
3-hexen-6-yl, 4-hexen-6-yl and the like.

The term "C₂-C₆ alkynyl" refers to straight or branched hydrocarbon chains containing 1 triple bond and from 2 to 6
30 carbon atoms and includes, but is not limited to,
acetylenyl, propynyl, 2-butyn-4-yl, 1-butyn-4-yl,
1-pentyn-5-yl, 2-pentyn-5-yl and the like.

The terms "C₁-C₆ alkoxy" and "C₁-C₄ alkoxy" refer respectively to a C₁-C₆ alkyl and C₁-C₄ alkyl group bonded

through an oxygen atom. The term "heteroaryloxy" refers to a heteroaryl or substituted heteroaryl group bonded through an oxygen atom. The term "aryloxy" refers to a phenyl or substituted phenyl group bonded through an oxygen atom. The 5 term "C₁-C₄ acyl" refers to a formyl group or a C₁-C₃ alkyl group bonded through a carbonyl moiety. The term "C₁-C₄ alkoxy carbonyl" refers to a C₁-C₄ alkoxy group bonded through a carbonyl moiety.

The term "halo" includes fluoro, chloro, bromo and 10 iodo.

The term "aryl" refers to an optionally substituted phenyl or optionally substituted heterocyclic ring.

The term "heterocyclic" is taken to mean an unsaturated 5- or 6-membered ring containing from 1 to 3 heteroatoms 15 selected from: nitrogen, oxygen and sulfur, said ring optionally being benzofused. Heterocyclic rings include furanyl, thienyl, pyridinyl, pyrrolyl, N-methylpyrrolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, triazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, pyrimidinyl, 20 pyrazinyl, pyridazinyl, and the like. Benzofused heterocyclic rings include isoquinolinyl, benzoxazolyl, benzthiazolyl, quinolinyl, benzofuranyl, benzothiophenyl, indolyl, and the like.

The terms "substituted phenyl" and "substituted 25 heterocycle" are taken to mean that the cyclic moiety in either case is substituted once with halo, cyano, nitro, C₁-C₄ acyl, trifluoromethane, trifluoromethoxy, C₁-C₄ alkoxy carbonyl, C₁-C₆ alkoxy, or C₁-C₄ alkyl, or two to five substituents independently selected from the halo group.

30 The term "amino protecting group" as used in this specification refers to a substituents commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. Examples of such amino-protecting groups include the formyl group, the trityl

group, the phthalimido group, the acetyl group, the trichloroacetyl group, the chloroacetyl, bromoacetyl, and iodoacetyl groups, urethane-type blocking groups such as benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl ("FMOC"), and the like; and like amino protecting groups. The species of amino protecting group employed is not critical so long as the derivitized amino group is stable to the condition of subsequent reactions on other positions of the molecule and can be removed at the appropriate point without disrupting the remainder of the molecule. Further examples of groups referred to by the above terms are described by T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1991, Chapter 7 hereafter referred to as "Greene".

15 The term "pharmaceutical" when used herein as an adjective, means substantially non-toxic and substantially non-deleterious to the recipient.

By "pharmaceutical formulation" it is further meant that the carrier, solvent, excipients and salt must be compatible with the active ingredient of the formulation (a compound of formula I).

20 The term "acid addition salt" refers to a salt of a compound of formula I prepared by reaction of a compound of formula I with a mineral or organic acid. For exemplification of pharmaceutical acid addition salts see, e.g., Berge, S.M., Bighley, L.D., and Monkhouse, D.C., *J. Pharm. Sci.*, 66:1, 1977. Since the compounds of this invention are amines, they are basic in nature and accordingly react with any of a number of inorganic and 25 organic acids to form pharmaceutical acid addition salts. Since some of the free amines of the compounds of this invention are typically oils at room temperature, it is preferable to convert the free amines to their pharmaceutically acceptable acid addition salts for ease of 30

handling and administration, since the latter are routinely solid at room temperature.

The pharmaceutical acid addition salts of the invention are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethylether, tetrahydrofuran, methanol, ethanol, isopropanol, benzene, and the like. The salts normally precipitate out of solution within about one hour to about 10 ten days and can be isolated by filtration or other conventional methods.

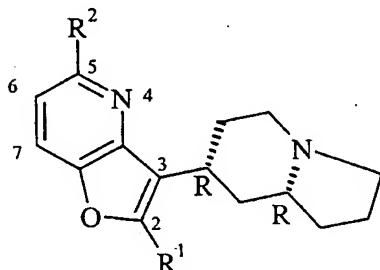
Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and Acids commonly employed to form such salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, 30 hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β -hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate

and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid, oxalic acid or fumaric acid.

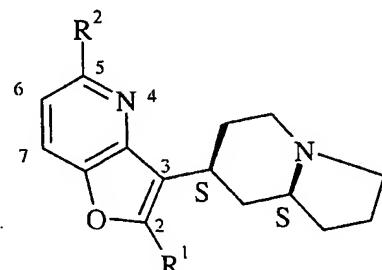
The term "effective amount" means an amount of a compound of formula I which is capable of activating 5-HT_{1F} receptors and/or inhibiting neuronal protein extravasation.

The term "suitable solvent" refers to any solvent, or mixture of solvents, inert to the ongoing reaction that sufficiently solubilizes the reactants to afford a medium within which to effect the desired reaction.

All enantiomers, diastereomers, and mixtures thereof, are included within the scope of the present invention. For example, the compounds of formula I where R is indolizidin-6-yl contain two chiral centers located in the bicyclic ring. One chiral center is located at the bridgehead carbon in the ring system, and the other is located in the CH group bonded to the 3-position of the indole ring. For the purposes of the present application, the numbering system for naming the substituents around the indole ring and the R,R and S,S enantiomers are illustrated below where R¹ and R² are as defined above.



R,R isomer



S,S isomer

The following group is illustrative of compounds contemplated within the scope of this invention:

- 1) 2-methyl-3-(2-[N', N'-diethylamino]ethyl)-5-(4-propanesulfonylbenzamide)furo[3,2-b]pyridine hydrochloride;
- 2) 2-n-butyl-3-(2-[N'-methyl-N'-benzylamino]ethyl)-5-(4-fluorobenzamide)furo[3,2-b]pyridine;
- 5) 2-isobutyl-3-(2-[N'-methyl-N'-cyclopropylmethyl-amino]ethyl)-5-(4-iodobenzamide)furo[3,2-b]pyridine naphthalene-1-sulfonate;
- 10) 2-s-butyl-3-(2-[N'-methyl-N'-(2-[1-propylpyrazol-4-yl]ethyl)amino]ethyl)-5-(4-fluorobenzamide)furo[3,2-b]pyridine ditoluoyltartrate;
- 15) 2-methyl-3-(2-[N'-methyl-N'-s-butylamino]ethyl)-5-isobutyramidefuro[3,2-b]pyridine;
- 6) 2-methyl-3-(2-[N'-methyl-N'-(2-[pyridin-4-yl]-ethyl)amino]ethyl)-5-(4-fluorobenzamide)furo[3,2-b]pyridine malonate;
- 7) 2-methyl-3-(2-[N'-methyl-N'-(2-[1-isopropylpyrazol-4-yl]ethyl)amino]ethyl)-5-butyramidefuro[3,2-b]pyridine mandelate;
- 20) 3-(2-[N'-methyl-N'-(4-bromothien-2-yl)methyl]amino)-ethyl)-5-(4-fluorobenzamide)furo[3,2-b]pyridine hydrochloride;
- 9) 2-ethyl-3-(2-[N'-ethyl-N'-(2-[3-methylthiobenzofur-5-yl]ethyl)amino]ethyl)-5-(pyridine-2-carboxamide)furo[3,2-b]pyridine;
- 25) 10) 2-propyl-3-(2-[N'-isopropyl-N'-(3-[isobenzofur-2-yl]propyl)amino]ethyl)-5-(4-fluorobenzamide)furo[3,2-b]pyridine;
- 11) 2-methyl-3-(2-[N'-butyl-N'-(pyrrol-3-yl)methyl]amino)ethyl)-5-(4-fluorobenzamide)furo[3,2-b]pyridine maleate;
- 30) 12) 2-methyl-3-(2-[N'-methyl-N'-(5-cyanoimidazol-2-yl)methyl]amino)ethyl)-5-acetamidefuro[3,2-b]pyridine trifluoroacetate;
- 13) 2-methyl-3-(2-[N'-methyl-N'-(6-carboxamidopyrazin-2-yl)methyl]amino)ethyl)-5-propanecarboxamidefuro[3,2-b]pyridine;

- 14) 2-methyl-3-(2-[N'-methyl-N'-(5-nitropyrimidin-2-yl)methyl]aminoethyl)-5-(2-propanecarboxamide)furo[3,2-b]pyridine;
- 15) 2-methyl-3-(2-[N'-methyl-N'-(5-dimethylaminopyridin-3-yl)methyl]aminoethyl)-5-butyramidefuro[3,2-b]pyridine benzoate;
- 16) 2-methyl-3-(2-[N'-methyl-N'-(indazol-5-yl)methyl]aminoethyl)-5-pantanecarboxamidefuro[3,2-b]pyridine;
- 17) 2-methyl-3-(2-[N'-methyl-N'-(quinolin-4-yl)methyl]aminoethyl)-5-cyclopropanecarboxamidefuro[3,2-b]pyridine;
- 18) 2-methyl-3-(2-[N'-methyl-N'-(isoquinolin-7-yl)methyl]aminoethyl)-5-cyclobutanecarboxamidefuro[3,2-b]pyridine;
- 19) 2-methyl-3-(2-[N'-methyl-N'-(quinoxalin-2-yl)methyl]aminoethyl)-5-cyclopantanecarboxamidefuro[3,2-b]pyridine hexanoate;
- 20) 2-methyl-3-(2-[N'-methyl-N'-(quinaxolin-5-yl)methyl]aminoethyl)-5-cyclohexanecarboxamidefuro[3,2-b]pyridine;
- 21) 2-methyl-3-(2-[N'-methyl-N'-(thiazol-2-yl)methyl]aminoethyl)-5-cycloheptanecarboxamidefuro[3,2-b]pyridine;
- 22) 2-methyl-3-(2-[N'-methyl-N'-(2-aminobenzothiazol-5-yl)methyl]aminoethyl)-5-(4-fluorobenzamide)furo[3,2-b]pyridine trifluoromethanesulfonate;
- 23) 2-methyl-3-(2-[N'-methyl-N'-(oxazol-5-yl)methyl]aminoethyl)-5-(3-iodobenzamide)furo[3,2-b]pyridine;
- 24) 2-methyl-3-(2-[N'-methyl-N'-(6-nitrobenzoxazol-2-yl)methyl]aminoethyl)-5-(2-chlorobenzamide)furo[3,2-b]pyridine hydrobromide;
- 25) 2-methyl-3-(2-[N'-methyl-N'-(1,4-benzodioxan-6-yl)methyl]aminoethyl)-5-(2-chloropyridine-3-carboxamide)furo[3,2-b]pyridine;
- 26) 2-isopropyl-3-(2-[N'-methyl-N'-(isoxazol-4-yl)methyl]aminoethyl)-5-benzamidefuro[3,2-b]pyridine;
- 27) 2-methyl-3-(2-[N'-methyl-N'-(benzisoxazol-3-yl)methyl]aminoethyl)-5-(thiophene-2-carboxamide)furo[3,2-b]pyridine;

- 28) 2-methyl-3-(2-[N'-methyl-N'-(1,3,4-oxadiazol-2-yl)-methyl]amino)ethyl)-5-(furyl-3-carboxamide)furo[3,2-b]pyridine;
- 29) 2-methyl-3-(2-[N'-methyl-N'-(1,2,3-triazol-4-yl)-methyl]amino)ethyl)-5-(4-fluorobenzamide)furo[3,2-b]pyridine tosylate;
- 30) 3-(2-[N'-methyl-N'-(4-bromothien-2-yl)methyl]amino)ethyl)-5-(4-fluorobenzamide)furo[3,2-b]pyridine hydrochloride
- 31) 2-ethyl-3-(2-[N'-ethyl-N'-(3-methylthiobenzofur-5-yl)ethyl]amino)ethyl)-5-(pyridine-2-carboxamide)furo[3,2-b]pyridine;
- 32) 2-propyl-3-(2-[N'-isopropyl-N'-1-((isobenzofur-2-yl)prop-3-yl)amino]ethyl)-5-(4-fluorobenzamide)furo[3,2-b]pyridine;
- 33) 2-methyl-3-(2-[N'-butyl-N'-(pyrrol-3-yl)methyl]amino)ethyl)-5-(4-fluorobenzamide)furo[3,2-b]pyridine maleate;
- 34) 2-methyl-3-(2-[N'-methyl-N'-(5-cyanoimidazol-2-yl)methyl]amino)ethyl)-5-(4-acetamide)furo[3,2-b]pyridine trifluoroacetate;
- 35) 2-methyl-3-(2-[N'-methyl-N'-(6-carboxamidopyrazin-2-yl)methyl]amino)ethyl)-5-propanecarboxamidefuro[3,2-b]pyridine;
- 36) 2-methyl-3-(2-[N'-methyl-N'-(5-nitropyrimidin-2-yl)methyl]amino)ethyl)-5-(2-propanecarboxamide)furo[3,2-b]pyridine;
- 37) 2-methyl-3-(2-[N'-methyl-N'-(5-dimethylaminopyridin-3-yl)methyl]amino)ethyl)-5-butanecarboxamidefuro[3,2-b]pyridine benzoate;
- 38) 2-methyl-3-(2-[N'-methyl-N'-(indazol-5-yl)methyl]amino)ethyl)-5-pentanecarboxamidefuro[3,2-b]pyridine;
- 39) 2-methyl-3-(2-[N'-methyl-N'-(2-aminobenzothiazol-5-yl)methyl]amino)ethyl)-5-(4-fluorobenzamide)furo[3,2-b]pyridine trifluoromethanesulfonate;
- 40) 2-methyl-3-(2-[N'-methyl-N'-(2-[pyridin-4-yl]ethyl)amino]ethyl)-5-(N-ethylurea)furo[3,2-b]pyridine;

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- 41) 2-methyl-3-(2-[N'-methyl-N'-s-butylamino]ethyl)-5-(N-isopropylurea)furo[3,2-b]pyridine;
- 42) 2-methyl-3-(2-[N'-methyl-N'-(2-[pyridin-4-yl]ethyl)amino]ethyl)-5-[N-[(3-methoxy)phenyl]urea]furo[3,2-b]pyridine malonate

While all enantiomers, diastereomers, and mixtures thereof, are useful as 5-HT_{1F} agonists, single enantiomers and single diastereomers are preferred. Furthermore, while 10 all of the compounds of this invention are useful as 5-HT_{1F} agonists, certain classes are preferred. The following paragraphs describe such preferred classes.

- 1) R is moiety (a);
- 15 2) R is moiety (b);
- 3) R is moiety (c);
- 4) E-D is CH-CH₂;
- 5) E-D is C=CH;
- 6) R¹ is hydrogen;
- 20 7) R¹ is C₁-C₄ alkyl;
- 8) R¹ is methyl;
- 9) R² is hydrogen;
- 10) R² is halo;
- 11) R² is hydroxy;
- 25 12) R² is -NR³R⁴;
- 13) R² is -SR³;
- 14) R² is -C(O)R³;
- 15) R² is -C(O)NR³R⁴;
- 16) R² is -NR³SO₂R⁵;
- 30 17) R² is -NHC(Q)NR³R⁴
- 18) R² is -NHC(Q)NR³R⁴, and Q is S;
- 19) R² is -NHC(Q)NR³R⁴, and Q is O;
- 20) R² is -NHC(O)OR³;
- 21) R² is -NR³C(O)R⁵;

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- 22) R² is -NR³R⁴ and R³ and R⁴ are taken together with
the nitrogen to which they are attached are
selected from the group consisting of pyrrolidine,
piperidine, piperazine, morpholine, or
thiomorpholine;
- 5 23) R³ is hydrogen;
- 24) R³ is C₁-C₄ alkyl;
- 25) R³ is methyl;
- 26) R³ is C₂-C₆ alkenyl;
- 10 27) R³ is C₂-C₆ alkynyl;
- 28) R³ is -(CH₂)_naryl;
- 29) R⁴ is hydrogen;
- 30) R⁴ is C₁-C₄ alkyl;
- 31) R⁴ is C₂-C₆ alkenyl;
- 15 32) R⁴ is C₂C₆ alkynyl;
- 33) R⁴ is -(CH₂)_naryl;
- 34) R⁵ is hydrogen;
- 35) when R is CH₂CH₂NR³R⁴, R³ is hydrogen and R⁴ is
methyl;
- 20 36) when R is CH₂CH₂NR³R⁴, R³ is methyl and R⁴ is
methyl; R² is selected from the group consisting of
benzoylamino, propanoylamino, 4-fluorobenzoylamino,
2-thienoylamino, and 2,4-difluorobenzoylamino;
- 37) R³ is methyl;
- 25 38) R³ is ethyl;
- 39) R³ is propyl;
- 40) R³ is isopropyl;
- 41) R³ is phenyl;
- 42) R³ is allyl;
- 30 43) R³ is phenyl monosubstituted with halo;
- 44) R³ is 4-fluorophenyl;
- 45) R³ is 4-chlorophenyl;
- 46) R³ is phenyl (C₁-C₄ alkylene)
- 47) R³ is benzyl;

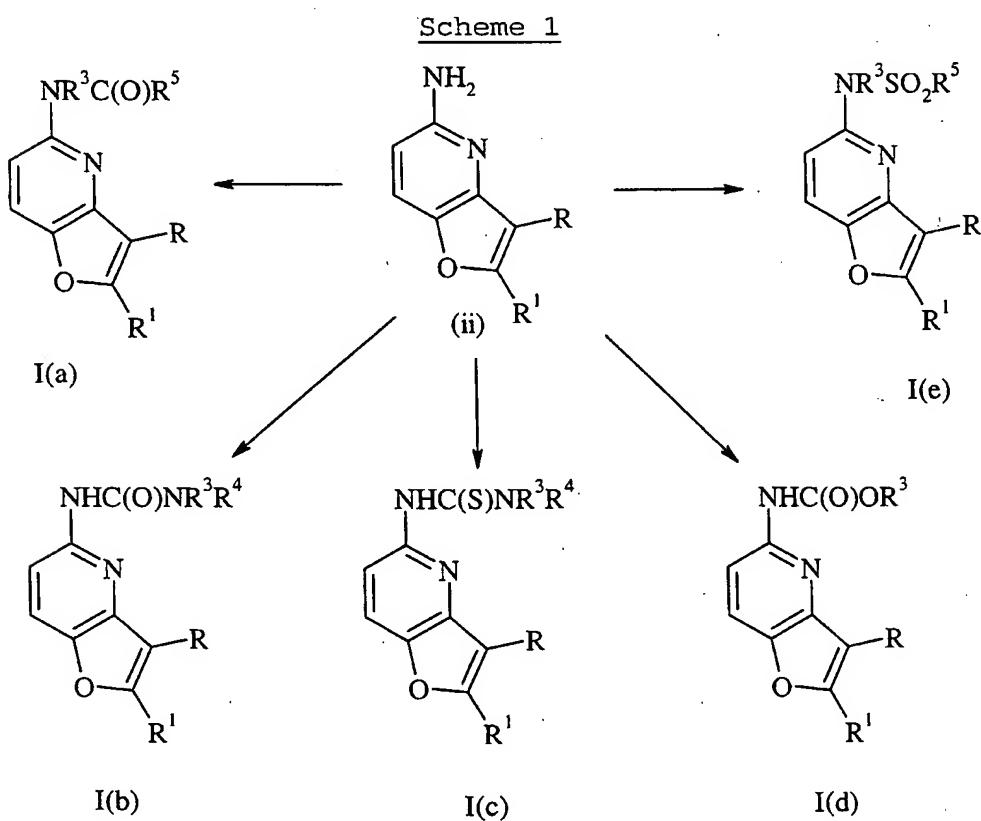
- 48) R³ is phenethyl;
- 49) R³ and R⁴ taken together with the nitrogen to which they are attached form a morpholine ring;
- 5 50) R³ and R⁴ taken together with the nitrogen to which they are attached form a thiomorpholine ring;
- 51) R³ and R⁴ taken together with the nitrogen to which they are attached form a pyrrolidine ring;
- 52) R³ and R⁴ taken together with the nitrogen to which they are attached form a piperidine ring;
- 10 53) R³ and R⁴ taken together with the nitrogen to which they are attached form a piperazine ring;
- 54) R³ and R⁴ taken together with the nitrogen to which they are attached form a 4-substituted piperazine ring;
- 15 55) R³ is methyl;
- 56) R³ is ethyl;
- 57) R³ is propyl;
- 58) R³ is allyl;
- 59) R³ is phenyl monosubstituted with C₁-C₄ alkoxy;
- 20 60) R³ is 4-methoxyphenyl;
- 61) R³ is phenyl;
- 62) any compound exemplified;
- 63) the compound is an acid addition salt;
- 64) the compound is the hydrochloride salt;
- 25 65) the compound is the oxalate salt; and
- 66) the compound is the fumarate salt.

It will be understood that the above classes may be combined to form additional preferred classes.

30 It is preferred that the mammal to be treated by the administration of compounds of this invention is human.

The synthetic methodology required to prepare the compounds of the invention is well known to those skilled in the art. A suitable electrophile is reacted with an

appropriate 5-aminofuro[3,2-b]pyridine to provide the corresponding ureas, thioureas, sulfonamides, carbamates, and carboxamides of the present invention. This chemistry is illustrated in Scheme 1 where R, R¹, R³, R⁴, and R⁵ are 5 as described *supra*.



10 To prepare compounds of the invention where R² is -NR³SO₂R⁵, formula I(e), a solution of the appropriate 5-aminofuro[3,2-b]pyridine in suitable solvent, such as tetrahydrofuran, dioxane, diethyl ether or dimethylformamide, at a temperature from about 0 °C to 15 about ambient, is reacted with a commercially available R⁵-sulfonyl halide or R⁵-sulfonic anhydride in the presence of a suitable base such as pyridine or triethylamine. The resultant sulfonamide may be isolated by dilution of the reaction mixture with water,

adjustment of pH, and extraction with a water immiscible solvent such as dichloromethane. The product may be used for further reactions as recovered, or may be purified by chromatography, or by recrystallization from a suitable 5 solvent.

Compounds of the invention where R² is -NHC(Q)NR³R⁴, I(b)/I(c), are prepared by treating a solution of the appropriate 5-aminofuro[3,2-b]pyridine (ii) in a suitable solvent, such as chloroform or dichloromethane, with an 10 appropriate isocyanate, isothiocyanate, carbamoyl chloride or carbamoyl bromide. Appropriate carbamoyl chlorides are available by treating an amine of formula NHR³R⁴ with phosgene. When a carbamoyl chloride or carbamoyl bromide is used, the reactions are performed in 15 the presence of a suitable base. Suitable bases include amines typically used as acid scavengers, such as pyridine or triethylamine, or commercially available polymer bound bases such as polyvinylpyridine. If necessary, an excess of the isocyanate, isothiocyanate, 20 carbamoyl chloride or carbamoyl bromide is employed to ensure complete reaction of the starting amine. The reactions are performed at about ambient to about 80 °C, for from about three hours to about three days. Typically, the product may be isolated by washing the 25 reaction mixture with water and concentrating the remaining organics under reduced pressure. When an excess of isocyanate, isothiocyanate, carbamoyl chloride or carbamoyl bromide has been used, however, a polymer bound primary or secondary amine, such as an 30 aminomethylated polystyrene, may be conveniently added to react with the excess reagent. Isolation of products from reactions where a polymer bound reagent has been used is greatly simplified, requiring only filtration of the reaction mixture and then concentration of the 35 filtrate under reduced pressure. The product from these reactions may be purified chromatographically or recrystallized from a suitable solvent if desired. The

skilled artisan will appreciate that compounds of the invention which are ureas may be converted into the corresponding thiourea by treatment with [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] (Lawesson's Reagent) or phosphorus pentasulfide.

Compounds of the invention where R^2 is $R^3C(O)NH-$ I(a) or $-NR^3C(O)OR^5$ I(d) are prepared by treating the desired 5-aminofuro[3,2-b]pyridine (ii) with either an appropriate carboxylic acid chloride, bromide or anhydride, or an 10 appropriately substituted chloroformate optionally in the presence of an acylation catalyst such as dimethylamino-pyridine, in the presence of a suitable base. Suitable bases include amines typically used as acid scavengers, such 15 as pyridine or triethylamine, or commercially available polymer bound bases such as polyvinylpyridine. When an excess of the electrophile is necessary to ensure complete reaction of the amine, a polymer bound primary or secondary amine, such as an aminomethylated polystyrene, may be 20 conveniently added to react with the excess reagent. Isolation of products from reactions where a polymer bound reagent has been used is greatly simplified, requiring only filtration of the reaction mixture to remove the polymer bound constituents, and then concentration of the filtrate 25 under reduced pressure to isolate the desired product. The product from these reactions may be purified chromatographically or recrystallized from a suitable solvent if desired.

Alternatively, compounds of the invention where R^2 is $-NR^3C(O)R^5$ I(a) or $-NHC(O)OR^3$ I(d) may be prepared by 30 reacting the 5-aminofuro[3,2-b]pyridine (ii) with an appropriate carboxylic acid in the presence of a typical peptide coupling reagent such as N,N'-carbonyldiimidazole (CDI), N,N'-dicyclohexyl-carbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride 35 (EDC). Polymer supported forms of carbodiimide peptide coupling reagents are useful for the preparation of compounds of the present invention. A polymer supported

form of EDC, for example, has been described (*Tetrahedron Letters*, **34**(48), 7685 (1993)). Additionally, a new carbodiimide coupling reagent, 1-(3-(1-pyrrolidinyl)-propyl)-3-ethylcarbodiimide (PEPC), and its corresponding 5 polymer supported forms have been discovered and are very useful for the preparation of the compounds of the present invention.

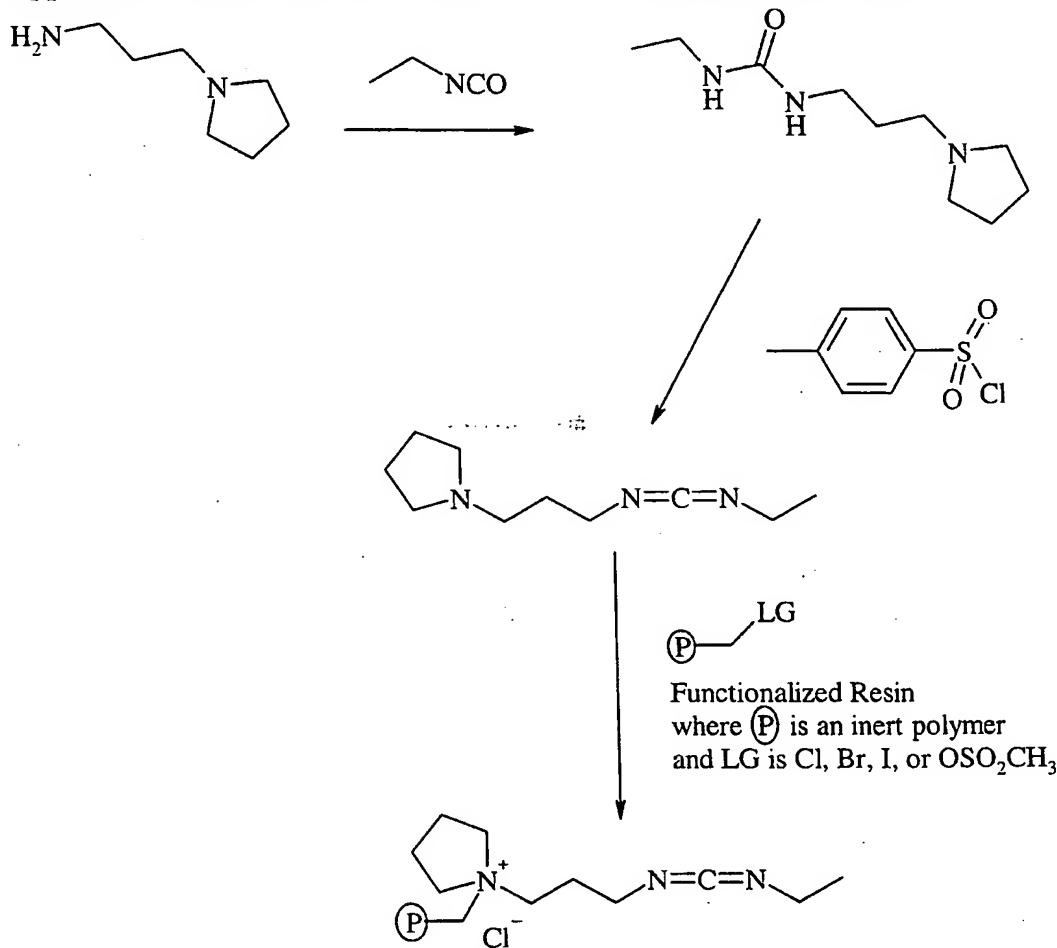
Polymers suitable for use in making a polymer supported coupling reagent are either commercially available or may be 10 prepared by methods well known to the artisan skilled in the polymer arts. A suitable polymer must possess pendant sidechains bearing moieties reactive with the terminal amine of the carbodiimide. Such reactive moieties include chloro, bromo, iodo and methanesulfonyl. Preferably, the reactive 15 moiety is a chloromethyl group. Additionally, the polymer's backbone must be inert to both the carbodiimide and reaction conditions under which the ultimate polymer bound coupling reagents will be used.

Certain hydroxymethylated resins may be converted into 20 chloromethylated resins useful for the preparation of polymer supported coupling reagents. Examples of these hydroxylated resins include the 4-hydroxymethyl-phenylacetamidomethyl resin (Pam Resin) and 4-benzyloxybenzyl alcohol resin (Wang Resin) available from 25 Advanced Chemtech of Louisville, KY (see Advanced Chemtech 1993-1994 catalog, page 115). The hydroxymethyl groups of these resins may be converted into the desired chloromethyl groups by any of a number of methods well known to the skilled artisan.

30 Preferred resins are the chloromethylated styrene/di-vinylbenzene resins because of their ready commercial availability. As the name suggests, these resins are already chloromethylated and require no chemical modification prior to use. These resins are commercially 35 known as Merrifield's resins and are available from Aldrich Chemical Company of Milwaukee, WI (see Aldrich 1994-1995 catalog, page 899).

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Methods for the preparation of PEPC and its polymer supported forms are outlined in the following scheme.



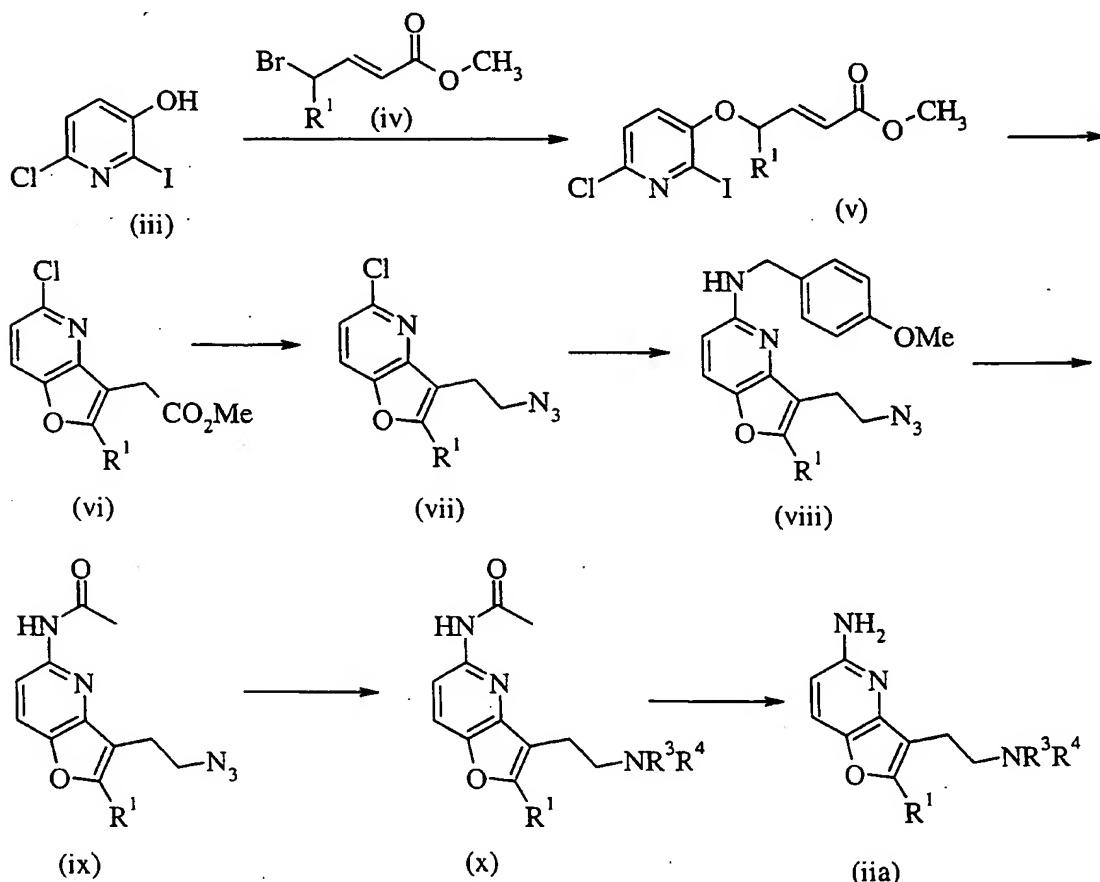
5 Briefly, PEPC is prepared by first reacting ethyl isocyanate with 1-(3-aminopropyl)pyrrolidine. The resulting urea is treated with 4-toluenesulfonyl chloride to provide PEPC. The polymer supported form is prepared by reaction of PEPC with an appropriate resin under standard conditions to give the desired reagent.

10 The carboxylic acid coupling reactions employing these reagents are performed at about ambient to about 45°C , for from about three hours to about three days. Typically, the product may be isolated by washing the reaction with water and concentrating the remaining organics under reduced pressure. As discussed supra, isolation of products from

reactions where a polymer bound reagent has been used is greatly simplified, requiring only filtration of the reaction mixture and then concentration of the filtrate under reduced pressure.

The 5-aminofuro[3,2-b]pyridines (ii) required for the preparation of the compounds of the present invention may be prepared by methods well known to one of ordinary skill in the art. Compounds of the invention where R is moiety (a) are derived from the corresponding 5-aminofuro[3,2-b]pyridines which may be prepared by the procedure described in Scheme 2 where R¹, R³ and R⁴ are as previously defined.

Scheme 2



6-Chloro-2-iodo-3-hydroxypyridine (iii) and an appropriate ester, such as methyl 4-bromocrotonate (iv) or

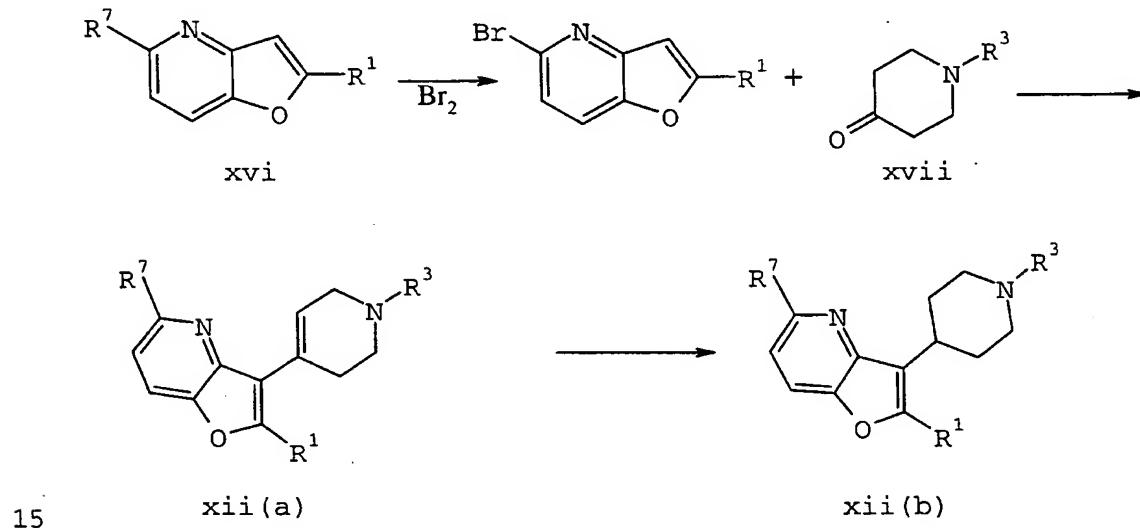
methyl 4-bromo-2-pentenoate, are combined in an appropriate solvent, typically tetrahydrofuran, dimethylformamide or N-methylpyrrolidinone with a suitable base, typically potassium or sodium carbonate, pyridine or triethylamine,
5 and the reaction mixture heated to reflux until all of the starting substituted pyridine has reacted. The resulting compound of formula (v) may then be used directly or purified by crystallization or chromatography. As the skilled artisan would appreciate, the compound of formula
10 (vi) may be prepared through a coupling reaction of a compound of formula (v), see Larock, et al., *Tetrahedron Letters*, 1988, 29:4687-4690.

Compounds of the invention where R is $-\text{CH}_2\text{CH}(\text{R}^5)\text{NR}^3\text{R}^4$ are prepared from compounds of formula (vi). One method of
15 such preparation may first consist of converting the ester to an alcohol and then converting the alcohol to an azidoalkane. Such methods may be found in Larock, *Comprehensive Organic Transformations*, 1989, pp 419. The resulting compound of formula (vii) may then be used
20 directly or purified by crystallization or chromatography. The resulting compound of formula (vii) may then be aminated at the halo group, see Buchwald, et al., *Journal of the American Chemical Society*, 1997, 119:10539-10540. The resulting compound of formula (viii) may then be used
25 directly or purified by crystallization or chromatography. The amine of formula (viii) may then be converted to amide of formula (ix) by procedures well known to the skilled artisan, see Larock, *Comprehensive Organic Transformations*, 1989, pp 859. The resulting compound of formula (ix) may
30 then be used directly or purified by crystallization or chromatography. The azide of formula (ix) may then be reduced by catalytic hydrogenation over palladium with an appropriate aldehyde and, if desired, purified by crystallization or chromatography. While the acetamide
35 moiety (x) may be hydrolyzed during the hydrogenation step, the desired 5-amino-furo[3,2-b]pyridine (iia) may be prepared in a separate hydrolysis step if necessary.

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The 6-chloro-3-hydroxy-2-iodopyridine compounds of formula iii may be prepared from commercially available 2-chloro-4-aminopyridine by well known methodology. The amine substituent of 2-chloro-4-aminopyridine may be first converted to the acetate ester via diazonium salt formation followed by quenching with acetic anhydride. The ester group may then be hydrolyzed under standard conditions; see for example, Greene, "Protective Groups in Organic Synthesis, pg. 162; to liberate the hydroxy group.

Scheme 3



For furo[3,2-b]pyridine compounds of formula xii(a) the reaction may be performed by first reacting a furo[3,2-b]pyridine of formula xvi where R⁷ is amino or preferably nitro with bromine in acetic acid. The reaction is typically performed at about 50°C for about 4 hours. After the bromination is substantially complete, the volatiles are then removed under reduced pressure and the residue is

subjected to an extractive work-up under basic conditions. The resulting 3-bromofuro[3,2-b]pyridine in diethyl ether is then treated with an alkyl lithium, typically n-butyl lithium, in the same solvent, below -100 °C to affect a metal-halogen exchange. After stirring at this temperature for about 1 hour, the reaction mixture is treated with an equivalent of an appropriate compound of formula xvii. Once the addition of the compound of formula xvii is complete, the reaction mixture is stirred below -78 °C for an additional 3 to 5 hours. It is critical, when R¹ is hydrogen, to maintain the reaction mixture at this temperature to avoid equilibration of the anion to the 2-position of the benzofuran ring. The reaction mixture is then allowed to warm to -20 °C over about 50 minutes. An excess of an appropriate base, preferably sodium or potassium hydroxide, in a lower alkanol, typically methanol or ethanol is then added and the reaction refluxed for 0.25 to 24 hours to provide a benzofuran compound of formula xii(a) where R⁷ is amino or nitro.

If desired, compounds of formula xii(a) may be hydrogenated over a precious metal catalyst to give the corresponding compounds of formula xii(b). When R⁷ is bromo, a catalyst such as sulfided platinum on carbon, platinum oxide, or a mixed catalyst system of sulfided platinum on carbon with platinum oxide may be used to prevent hydrogenolysis of that bromo substituent during the reduction. The hydrogenation solvent may consist of a lower alkanol, such as methanol or ethanol, tetrahydrofuran, or a mixed solvent system of tetrahydrofuran and ethyl acetate.

The hydrogenation may be performed at an initial hydrogen pressure of 20 p.s.i. to 80 p.s.i., preferably from 50 p.s.i. to 60 p.s.i., at 0°C to 60°C, preferably at ambient temperature to 40°C, for 1 hour to 3 days. Additional

charges of hydrogen may be required to drive the reaction to completion depending on the specific substrate.

When the hydrogenation is performed with a compound of formula xii(a) where R⁷ is amino or nitro, more vigorous 5 hydrogenation conditions may be used without disrupting the rest of the molecule. For example, a catalyst such as platinum or palladium on carbon may be utilized without substantially effecting deleterious side reactions.

In general, when R⁷ is nitro, that nitro group may be 10 reduced to an amine at any convenient point in the syntheses outlined in Scheme 3 by well known methodology. See, e.g., Larock, "Comprehensive Organic Transformations", pgs. 412-415, VCH Publishers, New York, N.Y., 1989. Additionally, when R⁷ is nitro in compounds of formula xii(a), that nitro group and 15 the double bond may be hydrogenated simultaneously if desired to give a compound of formula xii(b) where R⁷ is amino by many of the methods described by Larock for the nitro group alone. Furthermore, methods for selective reduction of a double bond 20 in the presence of a nitro group are known in the art.

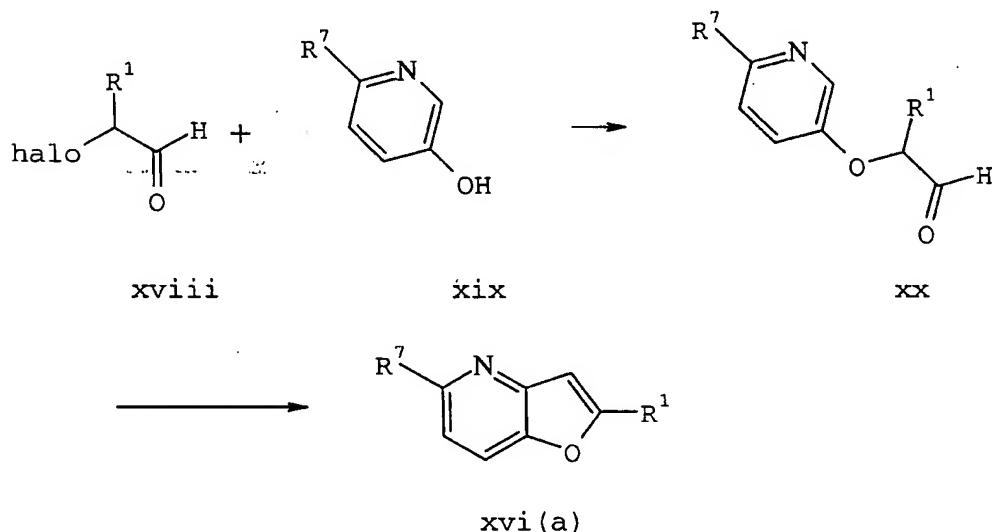
When R⁷ is amino, that amino group may be converted to an oxo group via methods well known to the skilled artisan at any convenient point in the syntheses outlined in Scheme 3. The amino group may first be treated with sodium nitrate and H⁺ and then with POBr₃ to convert the amino group to bromo. If 25 needed, it is preferred to perform the reaction after the conversion of a compound of formula xii(a) to a compound of formula xii(b).

When R⁷ is hydroxy, that free hydroxy group may have a trifluoromethanesulfonyl group (SO₂CF₃) installed by 30 standard procedures known in the art at any convenient point in the syntheses outlined in Scheme 3. For example, a compound of formula xii(a) where R⁷ is hydroxy may be reacted with trifluoromethanesulfonyl chloride or trifluoromethanesulfonic anhydride in the presence of an

appropriate base to give a compound of formula xii(a) where R⁷ is OSO₂CF₃.

Compounds of formula xvi may be prepared by known procedures such as that described in Scheme 4 below where R¹ and R⁷ are as defined above.

Scheme 4

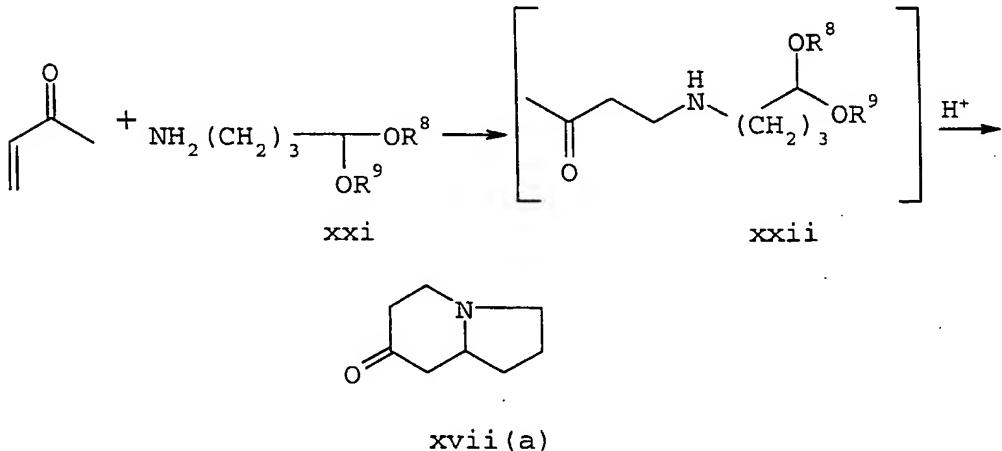


- 10 An α-halo-acetaldehyde of formula xviii, optionally protected as the corresponding acetal, may be reacted with an appropriately substituted, commercially available, hydroxypyridine of formula xix under standard alkylating conditions to provide the corresponding ether of formula X.
- 15 This ether may be converted to a benzofuran of formula xvi(a) by heating a compound of formula xx in the presence of an acid, typically polyphosphoric acid or sulfuric acid. When R⁷ is amino in compounds of formula xix or xx, that amino group should be protected with an appropriate amino protecting group as described in Greene. The protecting group may be chosen such that it is hydrolyzed during the cyclization step or, if desired, the unprotected compounds of formula xvi(a) where R⁷ is amino may be prepared in a

separate deprotection step if necessary. Furthermore, these amino compounds of formula xvi(a) may be converted to the corresponding halo compounds via the Sandmeyer reaction.

Compounds of formula xvii where R is an indolizine may
 5 be prepared from methylvinyl ketone and an appropriate
 amino-dialkylacetal or -cyclic acetal according to the
 procedures found in *Tet. Lett.*, 24:3281, 1983, and *J.C.S. Perk. I*, 447, 1986. These acetals are generally
 10 commercially available or can be synthesized by well known
 methods in the art from their corresponding commercially
 available 4-substituted butanals. This chemistry is
 illustrated in Scheme 5, R⁸ and R⁹ are C₁-C₄ alkyl or R⁸ and
 R⁹ taken together with the oxygen atoms, to which they are
 attached, form a 5 or 6 membered cyclic acetal.

15

Scheme 5

Compounds of formula xvii(a) may be prepared by
 20 acid treatment of the addition product of methyl vinyl
 ketone and a compound of formula xxi. A diethylacetal of
 formula xxi is a preferred starting material for this
 reaction (R⁹ and R⁸ are ethyl). The reaction may be
 performed by first dissolving an appropriate aminoacetal of
 25 formula xxiii in an suitable solvent, typically diethyl

ether at 0°C, and then adding approximately 1.7 equivalents of methyl vinyl ketone. Typically the reaction is allowed to stir at 0°C for approximately 2 hours before acidification by addition of, or extraction with, aqueous hydrochloric acid. Usually, the organic layer is removed before heating the aqueous layer to approximately 100°C for 1 hour. The resulting compounds of formula xvii(a) may be isolated from the reaction mixture by adjusting the pH of the solution to alkaline and extracting with a water immiscible solvent such as ethyl acetate or dichloromethane.

Compounds of formula xvii(a), prepared as described in Scheme 5 are racemic and, if used as described in Scheme 3 will produce racemic compounds of the invention.

Compounds of the invention that are optically enhanced in one enantiomer may be obtained by resolving the compounds of formula xvii(a) before use of these compounds as described in Scheme 5. Methods of resolving enantiomeric compounds of this type are well known in the art. For example, resolution can be achieved by use of chiral chromatography. Furthermore, racemic compounds of formula xvii(a) may be converted to their corresponding diastereomeric mixture of salts by reaction with a chiral acid such as (+) or (-) tartaric acid. The diastereomers may then be separated and purified by recrystallization. Once separated, the salts may each be converted back to the chiral free base compounds of formula xvii(a) by reacting the salts with an aqueous base, such as sodium hydroxide, then extracting the mixture with a common organic solvent. The optical purity in resolved compounds of formula xvii(a) is maintained while undergoing the chemistry described in this application to afford optically pure compounds of the invention. As an alternative, when advantageous, the resolution techniques just discussed may be performed at any convenient point in the syntheses described in Schemes 4 - 5.

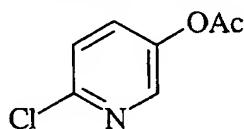
The α -halo aldehydes, or corresponding acetals of formula xviii are either commercially available or may be prepared from the corresponding acids or acid halides by methods well known to one of ordinary skill in the art.

- 5 This chemistry is reviewed by Larock, "Comprehensive Organic Transformations," pages 378-379, VCH Publishers, New York, 1989. Compounds of formula xiii, xvi, xvii, xviii, xix, and xxi are known in the art and, to the extent not commercially available, are readily synthesized by standard procedures
10 commonly employed in the art such as those described herein.

The optimal time for performing the reactions of Schemes 1-6 may be determined by monitoring the progress of the reaction via conventional chromatographic techniques, e.g., thin layer chromatography and high performance liquid chromatography. Furthermore, it is usually preferred to conduct the reactions of Scheme 1-6 under an inert atmosphere, such as, for example, argon, or, particularly, nitrogen. Choice of solvent is generally not critical so long as the solvent employed is inert to the ongoing reaction and sufficiently solubilizes the reactants to effect the desired reaction. The intermediate compounds of this invention are preferably purified before their use in subsequent reactions. The intermediates and final products may be purified when, if in the course of their formation, they crystallize out of the reaction solution. In such a situation, the precipitate may be collected by filtration and washed with an appropriate solvent. Certain impurities may be removed from the organic reaction mixture by aqueous acidic or basic extraction followed by removal of the solvent by extraction, evaporation, or decantation. The intermediates and final products of formula I may be further purified, if desired by common techniques such as recrystallization or chromatography over solid supports such as silica gel or alumina.

The following Preparations and Examples are provided to better elucidate the practice of the present invention and should not be interpreted in any way as to limit the scope
5 of same.

Preparation 1



2-Chloro-5-acetoxy pyridine

10

To a solution of 2-chloro-5-aminopyridine (30.0 g, 230 mmol) cooled to -10 °C in 120 mL of 3:1 1,2-dimethoxyethane/dichloromethane was added 62.1 mL of boron trifluoride diethyl etherate (490 mL) followed by a 15 solution of isobutyl nitrite (32.3 mL, 276 mmol) dissolved in 30 mL of 1,2-dimethoxyethane. The reaction was maintained at -10 °C for 0.25 h then allowed to warm to room temperature over 0.5 h. The mixture was diluted with pentane, cooled to 0 °C and filtered. The ivory solid was 20 washed with cold pentane, dried in vacuo, and used immediately without further purification.

30

The tetrafluoroborate diazonium salt was dissolved in 300 mL of acetic anhydride and heated at 75 °C for 2.5 h. The reaction was cooled, concentrated in vacuo, and partitioned between diethyl ether and saturated aqueous 5 NaHCO₃. The aqueous layer was extracted with diethyl ether, and the combined organics were washed with saturated aqueous NaCl, dried (MgSO₄), and concentrated in vacuo. The resulting brown residue was chromatographed (10% ethyl acetate/hexane) to provide 24.6 g (62%) of the desired 10 material as a white solid.

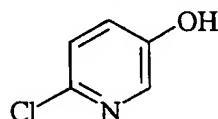
Calculated for C₇H₆ClNO₂:

Theory: C, 49.00; H, 3.52; N, 8.16;

Found: C, 49.29; H, 3.47; N, 8.12.

15

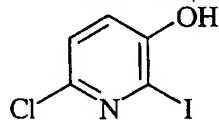
Preparation 2



2-Chloro-5-hydroxypyridine

2-Chloro-5-acetoxyppyridine (21.66 g, 126 mmol) was 20 dissolved in 300 mL of methanol and K₂CO₃ (8.70 g, 63 mmol) was added. The reaction was stirred at room temperature for approx. 2 h, then concentrated in vacuo. The residue was diluted with diethyl ether and water, and the aqueous layer was adjusted to neutral pH by the addition of 1N aqueous 25 HCl. Following extraction with diethyl ether, the organics were combined, washed with a solution of saturated aqueous NaCl, dried with MgSO₄, and concentrated in vacuo. The resulting yellow solid (15.58 g, 96%) was used without further purification.

31

Preparation 3

6-Chloro-2-iodo-3-hydroxypyridine

5 A solution of the above material (15.48 g, 119 mmol) and Na₂CO₃ (26.56 g, 251 mmol) in water (300 mL) was charged with iodine (30.3 g, 119 mmol). The reaction mixture was stirred at room temperature until the iodine color disappeared, approx. 48 h. The solution was adjusted to
10 pH = 5 with 1 N aqueous HCl, and extracted with ethyl acetate. The organic layers were washed with saturated aqueous NaCl, dried over Na₂SO₄, and concentrated in vacuo.

The resulting white solid was recrystallized from methanol to provide 17.8 g (95%) of the title compound.

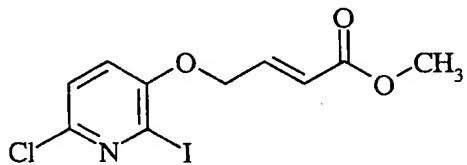
15 MS(m/e): 256 (M⁺)

Calculated for C₅H₃ClINO:

Theory: C, 23.51; H, 1.18; N, 5.48;

Found: C, 23.72; H, 1.19; N, 5.45.

20

Preparation 4

Methyl 4-(6-chloro-2-iodopyridyloxy)but-2-enoate

A mixture of 6-Chloro-2-iodo-3-hydroxypyridine (10.0 g,
25 39 mmol), methyl 4-bromocrotonate (14 mL, 117 mmol), and K₂CO₃ (16.2 g, 117 mmol) in 250 mL of *N,N*-dimethylformamide was heated at 60 °C for 4 h. The reaction was cooled, concentrated in vacuo and partitioned between chloroform and water. Following extraction with chloroform and washing

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with saturated aqueous NaCl, the organics were dried over Na₂SO₄ and concentrated in vacuo. Column chromatography (0%→30% ethyl acetate/hexane) provided the desired compound (13.3 g, 97%) as a white solid.

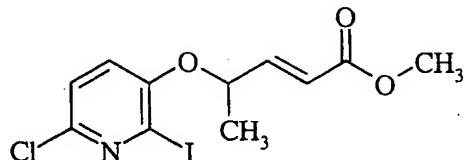
5 m.p. = 112-114 °C

Calculated for C₁₀H₉ClINO₃:

Theory: C, 33.97; H, 2.57; N, 3.96;
Found: C, 34.27; H, 2.72; N, 3.95.

10

Preparation 5



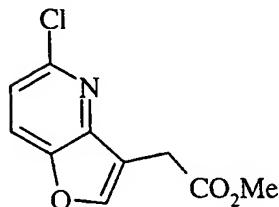
Methyl 4-(6-chloro-2-iodopyridyloxy)-4-methylbut-2-enoate

The title compound was prepared in 99% isolated yield
15 in the same manner as methyl 4-(6-chloro-2-iodopyridyloxy)
but-2-enoate, utilizing methyl 4-bromo-2-pentenoate
(Löffler, A. et al. Helv. Chim. Acta, 1970, 53, 403-417) as
the electrophile.

MS(m/e): 368 (M⁺)

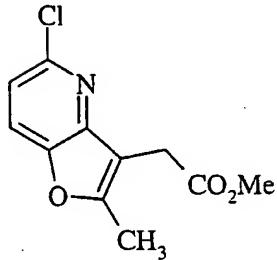
20 Calculated for C₁₁H₁₁ClINO₃:

Theory: C, 35.94; H, 3.02; N, 3.81;
Found: C, 35.70; H, 2.97; N, 3.81.

Preparation 6

3-Carbomethoxy-5-chlorofuro[3,2-b]pyridine

- 5 To a solution of methyl 4-(6-chloro-2-iodopyridyloxy) but-2-enoate (5.87 g, 16.6 mmol) dissolved in 150 mL of *N,N*-dimethylformamide was added 4.39 g of Na₂CO₃ (42 mmol), 1.13 g of sodium formate (16.6 mmol), 5.07 g of tetrabutylammonium chloride (18.0 mmol), and 0.19 g of palladium(II) acetate (0.8 mmol). The reaction mixture was heated at 80 °C for 3 h, then concentrated in vacuo. The residue was partitioned between chloroform and water, and the aqueous layer was extracted with chloroform. The combined organics were washed with saturated aqueous NaCl, dried over Na₂SO₄, and concentrated. Upon column chromatography (0%→40% ethyl acetate/hexane), the desired compound was isolated as an ivory solid (3.66 g, 98%).
m.p. = 92–93 °C
MS(m/e): 226 (M⁺)
- 10 15 20 Calculated for C₁₀H₈ClNO₃:
Theory: C, 53.23; H, 3.57; N, 6.21;
Found: C, 53.20; H, 3.61; N, 5.96.

Preparation 7

2-Methyl-3-carbomethoxy-5-chlorofuro[3,2-b]pyridine

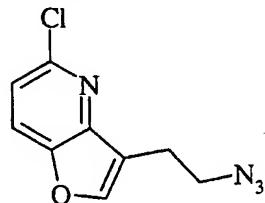
5 The title compound was prepared in 70% isolated yield
in the manner described in Preparation 6.

m.p. = 166-167 °C

MS(m/e): 240 (M⁺)

Calculated for C₁₁H₁₀ClNO₃:

10 Theory: C, 55.13; H, 4.21; N, 5.84;
Found: C, 55.18; H, 4.07; N, 6.07.

Preparation 8

15 3-(2-Azidoethyl)-5-chlorofuro[3,2-b]pyridine

To a solution of 3-carbomethoxy-5-chlorofuro[3,2-b]pyridine (3.0 g, 13 mmol) cooled to -78 °C in tetrahydrofuran (125 mL) was added diisobutylaluminum hydride (1 M in hexane, 40 mL, 40 mmol). The reaction mixture was maintained at -78 °C for 0.25 h, warmed to room temperature over a period of 1 h, then poured into a solution of 2 M aqueous sodium potassium tartrate. After stirring vigorously at room temperature overnight, the aqueous layer was extracted with ethyl

acetate. The combined organics were washed with saturated aqueous NaCl, dried over Na₂SO₄, and concentrated in vacuo.

The resulting crude alcohol was cooled to 0 °C in dichloromethane (150 mL), and charged with triethylamine 5 (4.1 mL, 29 mmol) followed by methanesulfonyl chloride (1.4 mL, 17 mmol). The reaction was warmed to room temperature and stirred for 2 h, then poured into a saturated solution of NaHCO₃. Following extraction with dichloromethane, the organic layer was washed with saturated 10 aqueous NaCl, dried over Na₂SO₄; and concentrated to provide an amber oil.

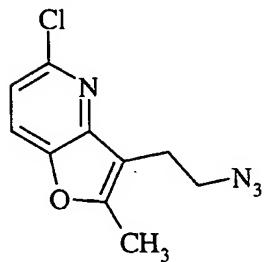
To the crude mesylate dissolved in N,N-dimethylformamide (100 mL) was added sodium azide (2.6 g, 40 mmol). The reaction was stirred at room temperature 15 overnight, then poured into water. The mixture was extracted with ethyl acetate, and the combined organics were washed with saturated aqueous NaCl, dried over Na₂SO₄, and concentrated. Column chromatography (0→20% ethyl acetate/hexane) provided the desired azide (2.4 g, 80%).

20 m.p. = 55–57 °C

Calculated for C₉H₇ClN₄O:

Theory: C, 48.55; H, 3.17; N, 25.17;

Found: C, 48.74; H, 3.13; N, 25.43.

Preparation 9

2-Methyl-3-(2-azidoethyl)-5-chlorofuro[3,2-b]pyridine

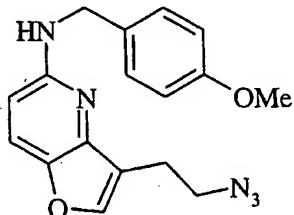
5 The title compound was prepared in 75% isolated yield
in the 3-step procedure described in Preparation 8.

MS (m/e): 237 (M⁺)

Calculated for C₁₀H₉ClN₄O:

Theory: C, 50.75; H, 3.83; N, 23.67;

10 Found: C, 50.75; H, 3.79; N, 23.65.

Preparation 10

15 3-(2-Azidoethyl)-5-(4-methoxyphenylmethylamino)furo-[3,2-b]pyridine

A solution of 3-(2-azidoethyl)-5-chlorofuro-[3,2-b]pyridine (2.32 g, 10.40 mmol) dissolved in toluene (300 mL) was treated with tris(dibenzylideneacetone)-
20 dipalladium(0) (0.48 g, 0.52 mmol), (\pm)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (0.65 g, 1.04 mmol), sodium *tert*-butoxide (1.40 g, 14.00 mmol), and 4-methoxybenzylamine (1.73 g, 12.00 mmol). The reaction was heated at 80 °C overnight. Upon cooling to room
25 temperature, the reaction was partitioned between ethyl

37

acetate and water. The aqueous layer was extracted with ethyl acetate, and the combined organics were washed with saturated aqueous NaCl, dried over Na₂SO₄, and concentrated. Column chromatography (0→25% ethyl acetate/hexane) provided 5 the title compound as a yellow oil (3.14 g, 93%).

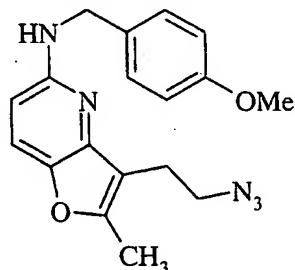
Calculated for C₁₇H₁₇N₅O₂:

Theory: C, 63.15; H, 5.30; N, 21.66;

Found: C, 63.55; H, 5.60; N, 21.33.

10

Preparation 11



2-Methyl-3-(2-azidoethyl)-5-(4-methoxyphenylmethylamino)furo[3,2-b]pyridine

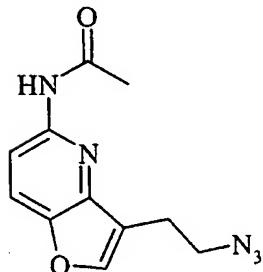
15 The title compound was prepared in 79% isolated yield from 2-methyl-3-(2-azidoethyl)-5-chlorofuro[3,2-b]pyridine in the manner described in Preparation 10.

MS(m/e): 338 (M⁺)

Calculated for C₁₈H₁₉N₅O₂:

20 Theory: C, 64.08; H, 5.68; N, 20.76;

Found: C, 64.10; H, 5.94; N, 20.75.

Preparation 12

5-Acetylaminomethylfuro[3,2-b]pyridine

5 To a rapidly stirring mixture of 3-(2-azidoethyl)-5-(4-methoxyphenylmethylamino)furo[3,2-b]pyridine (2.89 g, 8.9 mmol) dissolved in 300 mL of dichloromethane was added water (10 mL) followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (4.68 g, 20.5 mmol). After 2 h at room temperature, a solution of 1 M aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (100 mL) was added, and the reaction was stirred an additional 0.25 h. Following extraction with chloroform, the combined organics were washed with saturated aqueous NaCl , dried over Na_2SO_4 , and concentrated. The crude amine was purified via solid phase extraction (Varian Mega Bond Elut ® SCX column, eluting with 2 M ammonia-methanol), and concentrated in vacuo. The amine was dissolved in pyridine (250 mL) and treated with acetyl chloride (1.05 mL, 13.4 mmol). The reaction was heated at 55 °C for 3 h, then concentrated in vacuo. After partitioning between dichloromethane and 0.1 M aqueous NaOH , the aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with saturated aqueous NaCl , dried over Mg_2SO_4 , and concentrated in vacuo. Column chromatography on silica gel (0→80% ethyl acetate/hexane) provided the title compound (1.78 g, 81% yield) as a yellow solid.

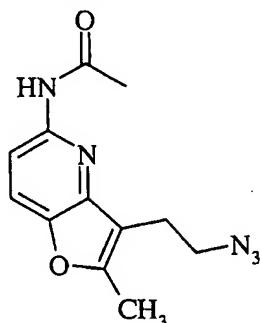
39

m.p. = 100-101 °C

MS(m/e): 246 (M^+)Calculated for $C_{11}H_{11}N_5O_2$:

Theory: C, 53.87; H, 4.52; N, 28.56;

5 Found: C, 53.96; H, 4.67; N, 28.33.

Preparation 132-Methyl-5-acetylamino-3-(2-azidoethyl)furo[3,2-b]pyridine
10

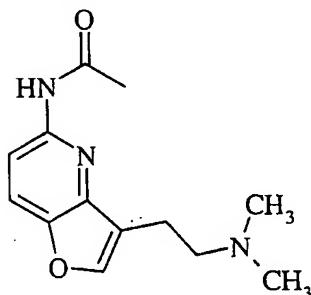
The title compound was prepared in 68% isolated yield from 2-methyl-3-(2-azidoethyl)-5-(4-methoxyphenylmethylamino)furo[3,2-b]pyridine using the method described in Preparation 12.

15 MS(m/e): 260 (M^+)Calculated for $C_{12}H_{13}N_5O_2$:

Theory: C, 55.59; H, 5.05; N, 27.01;

Found: C, 55.87; H, 5.17; N, 26.92.

40

Preparation 14

5-Acetylaminomethylfuro[3,2-b]pyridine

5

To a solution of 5-acetylaminomethylfuro[3,2-b]pyridine (1.65 g, 6.5 mmol) dissolved in ethanol (300 mL) was added 200 mg of 10% palladium on carbon. The mixture was hydrogenated at room temperature under 30 psi of hydrogen pressure for 2 h, filtered through celite, and concentrated in vacuo. The crude material was dissolved in methanol (180 mL), cooled to 0 °C, and treated with sodium cyanoborohydride (0.41 g, 16.2 mmol), acetic acid (2.0 mL, 32.4 mmol), and formaldehyde (37 wt. % in water, 1.66 mL, 19.5 mmol). The reaction was warmed to room temperature and stirred overnight. The solvent was removed, and the solid residue was partitioned between 3:1 chloroform/isopropyl alcohol and water. The aqueous layer was adjusted to pH = 14 with 1 N aqueous NaOH, extracted with chloroform, and the combined organics were washed with saturated aqueous NaCl,

41

dried over Na_2SO_4 , and concentrated. The residue was chromatographed on silica gel ($0 \rightarrow 20\%$ 2 M NH_3 -methanol/dichloromethane) to provide 1.26 g (79%) of the desired material. An analytical sample of the oxalate salt
5 was prepared.

m.p. = 168-170 °C

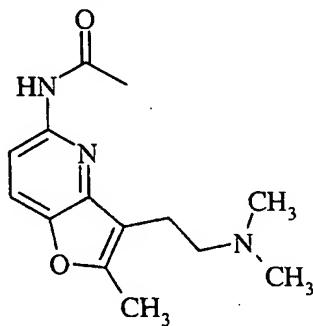
MS(m/e): 248 (M^+)

Calculated for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_2 \cdot \text{C}_2\text{H}_2\text{O}_4$:

Theory: C, 53.41; H, 5.68; N, 12.46;

10 Found: C, 53.57; H, 5.91; N, 12.57.

Preparation 15



15 5-Acetylaminomethylfuro[3,2-b]pyridine

The title compound was prepared from 5-acetylaminomethylfuro[3,2-b]pyridine in the manner described in Preparation 14 in 83% isolated yield.

20 m.p. = 138-139 °C

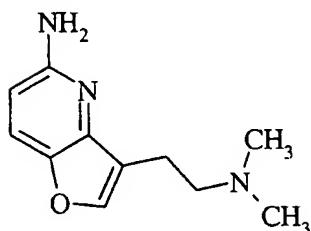
MS(m/e): 260 (M^+)

Calculated for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_2$:

Theory: C, 64.35; H, 7.33; N, 16.08;

Found: C, 64.14; H, 7.09; N, 16.07.

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Preparation 165-Amino-3-[2-(*N,N*-dimethylamino)ethyl]furo[3,2-b]pyridine

5 A solution of 5-acetylamo-3-[2-(*N,N*-dimethylamino)-ethyl]furo[3,2-b]pyridine (1.26 g, 5.10 mmol), dissolved in 120 mL of 1 *N* aqueous HCl was heated at 70 °C for 3 h. The reaction was cooled to room temperature, basified to pH > 12 with 5 *N* aqueous NaOH, and extracted with 3:1
10 chloroform/isopropyl alcohol. The combined organic extracts were washed with saturated aqueous NaCl, dried over Na₂SO₄, and concentrated. Chromatography (0→20% 2 *M* NH₃-methanol/dichloromethane) provided the desired material (85% yield) as white solid. A sample of the oxalate salt was
15 prepared for analysis.

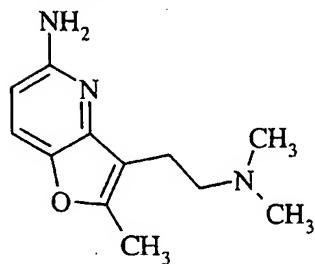
m.p. = 122-124 °C

MS(m/e): 206 (M⁺)

Calculated for C₁₁H₁₅N₃O·C₂H₂O₄·0.5 CH₄O:

Theory: C, 52.08; H, 6.15; N, 13.50;

20 Found: C, 52.03; H, 6.03; N, 13.51.

Preparation 17

5-Amino-3-[2-(*N,N*-dimethylamino)ethyl]-2-methylfuro-[3,2-b]pyridine

5

The title compound was prepared from 5-acetylamino-3-[2-(*N,N*-dimethylamino)ethyl]-2-methylfuro[3,2-b]pyridine in the same manner as 5-amino-3-[2-(*N,N*-dimethylamino)-ethyl]furo[3,2-b]pyridine, providing the title compound as
10 an amorphous white solid (79%).

m.p. = 103-104 °C

MS (m/e): 220 (M^+)

Calculated for $C_{12}H_{17}N_3O$:

Theory: C, 65.73; H, 7.81; N, 19.16;

15 Found: C, 65.65; H, 7.84; N, 18.93.

Example 1 & 2

5-amido-3-[2-(*N,N*-dimethylamino)ethyl]furo[3,2-b]pyridine
and 5-amido-3-[2-(*N,N*-dimethylamino)ethyl]-2-methylfuro[3,2-
20 b]pyridine

To a solution of the appropriate 5-aminofuro[3,2-b]pyridine prepared above (0.37 mmol) dissolved in 15 mL of pyridine was added the acid chloride (0.52 mmol). The
25 reaction mixture was heated at 55 °C for 2 h, then concentrated in vacuo. The residue was partitioned between 3:1 chloroform/isopropyl alcohol and 0.1 N aqueous NaOH. The aqueous layer was extracted with chloroform and the combined organics were washed with saturated aqueous NaCl,

dried over Na_2SO_4 , and concentrated. Chromatography (0→10% 2 M NH_3 -methanol/dichloromethane) provided the title compound which was analyzed either as the free base or converted to the oxalate salt.

5

Examples 3-12 were prepared and isolated in the same manner as Examples 1-2.

Example 3

10 3-[2-(*N,N*-Dimethylamino)ethyl]-5-propanoylamino furo[3,2-b]pyridine oxalate

The title compound was isolated in 83% yield as the oxalate salt.

15 m.p. = 153-155 °C

Calculated for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_2 \cdot \text{C}_2\text{H}_2\text{O}_4 \cdot 0.5 \text{CH}_4\text{O}$:

Theory: C, 54.31; H, 6.17; N, 11.69;

Found: C, 54.38; H, 6.19; N, 11.35.

20

Example 4

5-Benzoyl amino-3-[2-(*N,N*-dimethylamino)ethyl] furo[3,2-b]pyridine oxalate

The title compound was isolated in 73% yield as the 25 oxalate salt.

m.p. = 65-66 °C

Calculated for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2 \cdot \text{C}_2\text{H}_2\text{O}_4$:

Theory: C, 60.14; H, 5.30; N, 10.52;

Found: C, 60.39; H, 5.45; N, 10.46.

30

Example 5

3-[2-(*N,N*-Dimethylamino)ethyl]-5-(4-fluorobenzoyl)-aminofuro[3,2-b]pyridine oxalate

45

The title compound was isolated in 80% yield as the oxalate salt.

m.p. = 124-126 °C

MS(m/e): 328 (M⁺)

5 Calculated for C₁₈H₁₈FN₃O₂·C₂H₂O₄:

Theory: C, 57.55; H, 4.83; N, 10.07;

Found: C, 57.85; H, 4.95; N, 10.15.

Example 6

10 3-[2-(N,N-Dimethylamino)ethyl]-5-(2-thienoyl) aminofuro[3,2-b]pyridine oxalate

The title compound was isolated in 83% yield as the oxalate salt.

15 m.p. = 68-69 °C

MS(m/e): 330 (M⁺)

Calculated for C₁₆H₁₇N₃O₂S·C₂H₂O₄:

Theory: C, 53.33; H, 4.72; N, 10.36;

Found: C, 53.51; H, 4.64; N, 10.34.

20

Example 7

5-(2,4-Difluorobenzoyl)amino-3-[2-(N,N-dimethylamino)ethyl]furo[3,2-b]pyridine oxalate

25 The title compound was isolated in 90% yield as the oxalate salt.

MS(m/e): 346 (M⁺)

Example 8

30 3-[2-(N,N-Dimethylamino)ethyl]-2-methyl-5-propanoylamino furo[3,2-b]pyridine oxalate

The title compound was isolated in 80% yield as the oxalate salt.

46

m.p. = 168-170 °C

MS(m/e): 276 (M⁺)Calculated for C₁₄H₁₉N₃O₂·C₂H₂O₄·0.5 CH₄O:

Theory: C, 55.11; H, 6.61; N, 11.02;

5 Found: C, 55.31; H, 6.54; N, 10.81.

Example 95-Benzoylamino-3-[2-(N,N-dimethylamino)
ethyl]-2-methylfuro[3,2-b]pyridine

10

The title compound was isolated in 74% yield as the free base.

m.p. = 119-120 °C

MS(m/e): 324 (M⁺)15 Calculated for C₁₉H₂₁N₃O₂:

Theory: C, 70.57; H, 6.55; N, 12.99;

Found: C, 70.32; H, 6.81; N, 12.92.

Example 1020 3-[2-(N,N-Dimethylamino)ethyl]-5-(4-fluorobenzoyl)
amino-2-methylfuro[3,2-b]pyridine oxalate

The title compound was isolated in 80% yield as the oxalate salt.

25 m.p. = 136-138 °C

MS(m/e): 342 (M⁺)Calculated for C₁₄H₁₉N₃O₂·C₂H₂O₄·0.25 CH₄O:

Theory: C, 58.08; H, 5.28; N, 9.56;

Found: C, 57.33; H, 5.05; N, 9.28.

30

Example 11

3-[2-(*N,N*-Dimethylamino)ethyl]-2-methyl-5-(2-thienoyl)
aminofuro[3,2-b]pyridine oxalate

5 The title compound was isolated in 90% yield as the
oxalate salt.

m.p. = 211-212 °C

MS(m/e): 330 (M^+)

Calculated for $C_{17}H_{19}N_3O_2S \cdot C_2H_2O_4$:

10 Theory: C, 54.41; H, 5.05; N, 10.02;
Found: C, 54.65; H, 4.97; N, 10.06.

Example 12

15 5-(2,4-Difluorobenzoyl)amino-3-[2-(*N,N*-dimethylamino)
ethyl]-2-methylfuro[3,2-b]pyridine

The title compound was isolated in 74% yield as the
free base.

MS(m/e): 360 (M^+).

20 The type of formulation employed for the administration
of the compounds employed in the methods of the present
invention may be dictated by the particular compounds
employed, the type of pharmacokinetic profile desired from
25 the route of administration and the compound(s), and the
state of the patient.

Formulations amenable to oral or injectable
administration are prepared in a manner well known in the
pharmaceutical art and comprise at least one active
30 compound. See, e.g., REMINGTON'S PHARMACEUTICAL SCIENCES, (16th
ed. 1980).

In general, a formulation of the present invention
includes an active ingredient (a compound of formula I) and
is usually mixed with an excipient, diluted by an excipient

or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle,
5 carrier or medium for the active ingredient. Thus, the formulations can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by
10 weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size
15 prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a
20 substantially uniform distribution in the formulation, e.g., about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium
25 silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents
30 such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compounds of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after

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administration to the patient by employing procedures known in the art.

The following formulation examples are illustrative only and are not intended to limit the scope of the present
5 invention. The term "active ingredient" refers to a compound of formula I.

Formulation Example 1

Hard Gelatin Capsules

10

	<u>Quantity</u>
	<u>(mg/capsule)</u>
2-methyl-3-(2-[N'-methyl-N'-s-	
butylamino]ethyl)-5-isobutyramide-	
15 furo[3,2-b]pyridine	30.0
Starch	305.0
Magnesium stearate	5.0

The above ingredients are mixed and filled into hard
20 gelatin capsules in 340 mg quantities.

50

Formulation Example 2

Tablet

		Quantity (mg/tablet)
5	<u>Ingredient</u>	
	2-methyl-3-(2-[N'-methyl-N'-(2-[pyridin-4-yl]-ethyl)amino]-ethyl)-5-(4-fluorobenzamide)furo-[3,2-b]pyridine malonate	
10	Cellulose, microcrystalline	25.0
	Colloidal silicon dioxide	200.0
	Stearic acid	10.0
		5.0

The components are blended and compressed to form
15 tablets, each weighing 240 mg.

Formulation Example 3

Dry Powder Inhaler

	<u>Ingredient</u>	<u>Weight %</u>
20	2-methyl-3-(2-[N'-methyl-N'-(2-aminobenzothiazol-5-yl)-methyl]amino)ethyl)-5-(4-fluorobenzamide)-furo[3,2-b]pyridine	
25	Lactose	5
		95

The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation Example 4

Tablet

5	<u>Quantity</u>
<u>Ingredient</u>	<u>(mg/tablet)</u>
2-methyl-3-(2-[N'-methyl-N'-([thiazol-2-yl]methyl)amino]ethyl)- 5-cycloheptanecarboxamidefuro-	
10 [3,2-b]pyridine	30.0
Starch	45.0
Microcrystalline cellulose	35.0
Polyvinylpyrrolidone (as 10% solution in water)	4.0
15 Sodium carboxymethyl starch	4.5
Magnesium stearate	0.5
Talc	1.0
Total	120 mg

20 The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50°C-60°C and passed

25 through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

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Formulation Example 5

Capsules

		Quantity
	<u>Ingredient</u>	<u>(mg/capsule)</u>
5	2-methyl-3-(2-[N'-methyl-N'-(2-[1-isopropylpyrazol-4-yl]-ethyl)amino]ethyl)-5-	
10	butyramidefuro[3,2-b]pyridine	40.0
	Starch	109.0
	Magnesium stearate	1.0
	Total	150.0 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Formulation Example 6

20 Suppositories

	<u>Ingredient</u>	<u>Amount</u>
25	3-(2-[N'-methyl-N'-(4-bromothien-2-yl)methyl]-amino)ethyl)-5-(4-fluorobenzamide)furo[3,2-b]pyridine	25 mg
	Saturated fatty acid glycerides to 2,000 mg	

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Formulation Example 7

Suspensions

	<u>Ingredient</u>	<u>Amount</u>
5	2-ethyl-3-(2-[N'-ethyl-N'-(2-[3-methylthiobenzofur-5-yl]ethyl)-amino]ethyl)-5-(pyridine-2-carboxamide)furo[3,2-b]pyridine; Xanthan gum	50.0 mg 4.0 mg
10	Sodium carboxymethyl cellulose (11%) Microcrystalline cellulose (89%)	50.0 mg
	Sucrose	1.75 g
	Sodium benzoate	10.0 mg
	Flavor and color	q.v.
15	Purified water to	5.0 ml

The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Formulation Example 8

Capsules

		Quantity (mg/capsule)
5	<u>Ingredient</u>	
	2-propyl-3-(2-[N'-isopropyl-N'- (3-[isobenzofur-2-yl]propyl)amino]- ethyl)-5-(4-fluorobenzamide)-	
10	furo[3,2-b]pyridine	15.0
	Starch	407.0
	Magnesium stearate	<u>3.0</u>
	Total	425.0 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425 mg quantities.

Formulation Example 9

20 Intravenous Formulation

	<u>Ingredient</u>	<u>Quantity</u>
	2-methyl-3-(2-[N'-butyl-N'- ([pyrrol-3-yl)methyl]amino]ethyl)-	
25	5-(4-fluorobenzamide)furo-	
	[3,2-b]pyridine	250.0 mg
	Isotonic saline	1000 ml

Formulation Example 10

Topical Formulation

	<u>Ingredient</u>	<u>Quantity</u>
5	2-methyl-3-(2-[N'-methyl-N'-(([5-cyanoimidazol-2-yl)methyl)amino]- ethyl)-5-acetamidefuro[3,2-b]pyridine	1-10 g
	Emulsifying wax	30 g
	Liquid paraffin	20 g
10	White soft paraffin	to 100 g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

Formulation Example 11
Sublingual or Buccal Tablets

	<u>Ingredient</u>	<u>Quantity</u> (mg/tablet)
20		
25	2-methyl-3-(2-[N'-methyl-N'-(([isoquinolin-7-yl)methyl)amino]ethyl)-5- cyclobutanecarboxamidefuro-	
	[3,2-b]pyridine	10.0
	Glycerol	210.5
	Water	143.0
	Sodium citrate	4.5
30	Polyvinyl alcohol	26.5
	Polyvinylpyrrolidone	15.5
	Total	410.0 mg

The glycerol, water, sodium citrate, polyvinyl alcohol, and polyvinylpyrrolidone are admixed together by continuous

stirring and maintaining the temperature at about 90°C. When the polymers have gone into solution, the solution is cooled to about 50-55°C and the active ingredient is slowly admixed. The homogenous mixture is poured into forms made 5 of an inert material to produce a drug-containing diffusion matrix having a thickness of about 2-4 mm. This diffusion matrix is then cut to form individual tablets having the appropriate size.

While it is possible to administer a compound employed 10 in the methods of this invention directly without any formulation, the compounds are usually administered in the form of pharmaceutical compositions comprising a pharmaceutically acceptable excipient and at least one active ingredient. These formulations can be administered 15 by a variety of routes including oral, buccal, rectal, intranasal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Many of the compounds employed in the methods of this invention are effective as both injectable and oral compositions.

20 In order to administer transdermally, a transdermal delivery device ("patch") is needed. Such transdermal patches may be used to provide continuous or discontinuous infusion of a compound of the present invention in controlled amounts. The construction and use of transdermal 25 patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent No. 5,023,252, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

30 Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier.

One such implantable delivery system, used for the transport of biological factors to specific anatomical regions of the body, is described in U.S. Patent 5,011,472, which is herein incorporated by reference. The delivery of hydrophilic
5 drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

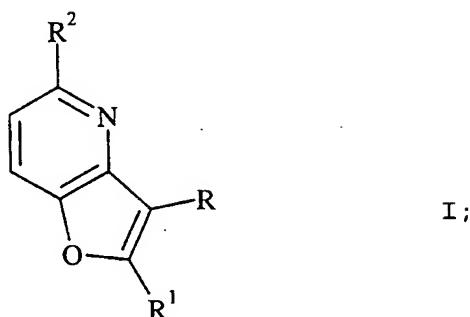
A compound of formula I is preferably formulated in a unit dosage form, each dosage containing from about 0.001 to
10 about 100 mg, more usually about 1.0 to about 30 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to
15 produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient as described above.

The active compounds are generally effective over a wide dosage range. For examples, dosages per day normally fall within the range of about 0.0001 to about 30 mg/kg of
20 body weight. In the treatment of adult humans, the range of about 0.1 to about 15 mg/kg/day, in single or divided dose, is especially preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant
25 circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not
30 intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the

aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several smaller doses for administration throughout the day.

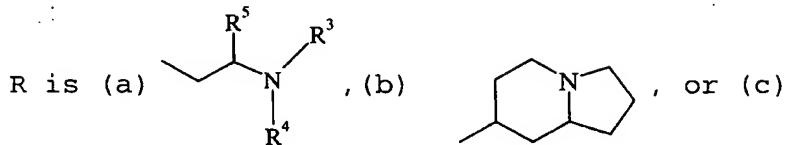
WE CLAIM:

1. A compound of formula I:

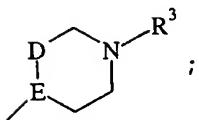


5

and pharmaceutical acid addition salts thereof, where;



10

E-D is C=CH or CH-CH₂;R¹ is hydrogen or C₁-C₄ alkyl;

R² is hydrogen, halo, hydroxy, -NR³R⁴, -SR³, -C(O)R³, -C(O)NR³R⁴, -NR³SO₂R⁵, -NHC(Q)NR³R⁴, -NHC(O)OR³, or
15 -NR³C(O)R⁵;

10 R³, R⁴, and R⁵ are independently hydrogen, C₁-C₄ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or -(CH₂)_naryl; or R³ and R⁴ combine, together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, piperazine, 4-20 substituted piperazine, morpholine, or thiomorpholine ring;
n is 0, 1, 2, 3, 4, 5, or 6; and
Q is O or S.

60

2. The compound of Claim 1 where R is moiety (a).

3. The compound of any one of Claims 1-2 where R³ is C₁-C₄ alkyl.

5

4. The compound of any one of Claims 1-3 where R⁴ is C₁-C₄ alkyl.

10 5. The compound of any one of Claims 1-4 where R¹ is methyl.

6. The compound of any one of Claims 1-5 where R³ is methyl and R⁴ is methyl.

15 7. A pharmaceutical formulation comprising a compound of any of Claims 1-6 and a pharmaceutical carrier, diluent, or excipient.

20 8. A method for activating 5-HT_{1F} receptors in a mammal comprising administering to a mammal in need of such activation an effective amount of a compound of any of Claims 1-6.

25 9. The method according to Claim 8 where the mammal is a human.

30 10. A method for inhibiting neuronal protein extravasation in a mammal comprising administering to a mammal in need of such inhibition an effective amount of a compound of any of Claims 1-6, or a pharmaceutical acid addition salt thereof.

11. The method according to Claim 10 where the mammal is a human.

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(57) Abstract: The present invention relates to a compound of formula (I) or a pharmaceutical acid addition salt thereof, which are useful for activating 5-HT_{1F} receptors and inhibiting neuronal protein extravasation in a mammal.

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International Application No

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	EP 0 832 650 A (LILLY CO ELI) 1 April 1998 (1998-04-01) abstract; claims; examples	1,7-11
A	EP 0 737 685 A (ADIR ET COMPAGNIE, FR.) 16 October 1996 (1996-10-16) page 50; example 75 page 52 -page 54 claims	1,7



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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